Phase II Study of Carboplatin Combined with Biweekly Docetaxel for Advanced Non-small Cell Lung Cancer

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Background: The combination of carboplatin and docetaxel has been considered one of the standard treatments for advanced non-small cell lung cancer (NSCLC). To investigate a safer and more convenient schedule for outpatient, we conducted a phase II study to evaluate the efficacy and the safety of carboplatin plus biweekly docetaxel for advanced NSCLC.

Patients and Methods: Patients with stage IIIB, IV, or postoperative recurrent NSCLC with good performance status were administered docetaxel at a dose of 35 mg/m^2 on days 1 and 15 and carboplatin at an area under the curve (AUC) of 6 on day 1 every 4 weeks for at least three cycles.

Results: Fifty patients were treated with median of three cycles (range 1–6). Grade 3/4 toxicities included neutropenia in 18 patients (36%), thrombocytopenia in 4 patients (8%), and anemia in 10 patients (20%). No patient experienced febrile neutropenia. Nonhematological toxicities were also mild to moderate, and there were no treatment-related deaths. The overall response rate was 30%, and the disease control rate was 70%. Among the elderly population, 54% of patients achieved partial response. Median progression-free survival was 4.8 months, and median overall survival was 11.8 months.

Conclusions: Biweekly docetaxel plus carboplatin has a similar efficacy and lower toxicity compared with a standard triweekly regimen of docetaxel plus carboplatin, which is a suitable regimen for outpatients, including elderly patients.

Key Words: Chemotherapy, Docetaxel, Biweekly, Carboplatin, Phase II trial, Non-small cell lung cancer.

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Lung cancer is the leading cause of cancer-related deaths in Japan and throughout the Western world.[1] Although chemotherapy for metastatic non-small cell lung cancer (NSCLC) had been considered ineffective and toxic, a meta-analysis of randomized controlled trials has shown that chemotherapy containing cisplatin improved the 1-year survival rate by 10% and prolonged median survival by 1.5 months compared with best supportive care.[2] Since new drugs including taxanes, gemcitabine, and vinorelbine have become available, the combination of one of these agents and a platinum compound has been considered the standard chemotherapy regimen for metastatic NSCLC.[3]

One of these platinum compounds, cisplatin, requires hydration to prevent renal damage and is therefore not indicated in the treatment of outpatients. To alleviate the renal toxicity of cisplatin, carboplatin was developed as a second-generation platinum compound. In NSCLC, the antitumor effect of carboplatin was found to be almost equal to that of cisplatin,[4] although meta-analyses suggested that cisplatin was slightly superior to carboplatin, at least in terms of response.[5,6] Because carboplatin does not induce renal damage or emesis, it is suitable for outpatient-based chemotherapy.

Carboplatin and docetaxel have different mechanisms of antitumor action, and most of their toxicities do not overlap. In addition, because docetaxel and platinum compounds do not have cross-tolerance, their combination may have higher efficacy than either alone. A randomized phase III study showed no difference in efficacy between docetaxel/carboplatin and cisplatin/vinorelbine.[7] Other studies have reported that docetaxel plus carboplatin had response rates of 39 and 43% and tolerable toxicity.[8,9]

When given at a dose of 60 to 70 mg/m^2, docetaxel is usually administered at intervals of 3 to 4 weeks. In contrast, weekly administration of docetaxel, divided into doses of 25 to 40 mg/m^2 for 3 to 6 weeks, had less hematological toxicity,[10,11] but docetaxel-induced pneumonitis was more frequent.[12] Biweekly administration of docetaxel is an attractive alternative because it seems to be safe, effective, and convenient for outpatient-based chemotherapy. As a result of our previous phase I study, docetaxel at a dose of 35 mg/m^2 on days 1 and 15 with carboplatin at an area under the curve (AUC) of 6 on day 1 were recommended for the phase II trial.[13] We therefore designed this phase II trial of biweekly docetaxel combined with carboplatin for patients with advanced NSCLC.

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PATIENTS AND METHODS

Patient Eligibility

The study population consisted of untreated patients older than 20 years of age with cytologically or histologically confirmed NSCLC of stage IIIB with pleural effusion, stage IV, or postoperative recurrence with distant metastasis. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 and a life expectancy of more than 3 months. Laboratory requirements included hemoglobin >9 g/dl, white blood cell count >4000/mm^3, neutrophils >2000/mm^3, platelets >100,000/mm^3, total bilirubin <1.5 mg/dl, transaminase <1.5 times the institutional upper limit of the normal value, serum creatinine <1.5 mg/dl, and PaO_2 >60 mm Hg. Patients were ineligible if they had symptomatic brain metastases, active double cancer, or a severe comorbidity contraindicating chemotherapy, such as symptomatic cardiovascular disease, uncontrolled diabetes, pulmonary fibrosis obvious in a chest x-ray, or a severe infectious disease. An institutional review board of each hospital approved this study, and written informed consent was obtained from each patient.

Drug Administration and Modification

During each 28-day cycle, docetaxel (35 mg/m^2) was administered intravenously on days 1 and 15, with intravenous carboplatin (AUC 6) administered immediately afterward on day 1. The carboplatin dose was calculated using the Calvert formula, with creatinine clearance estimated by the Cockroft–Gault equation. Before administration of anticancer agents, each patient received antiemetic agents consisting of 8 mg of dexamethasone and a 5-HT_3 antagonist intravenously. No prophylactic granulocyte colony–stimulating factor or prophylactic antibiotic support was planned.

Toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria version 2.0. Docetaxel on day 15 was administered when the neutrophil count was more than 1000/mm^3 and the platelet count was more than 75,000/mm^3. Dose reduction in subsequent cycles was permitted in cases of carboplatin reduced to AUC 5 with grade 4 neutropenia lasting 4 days, febrile neutropenia <1000/mm^3, thrombocytopenia <20,000/mm^3 or the need for platelet transfusion, or if a major nonhematological toxicity of at least grade 3, excluding anorexia or nausea. If such toxicities were still observed, the docetaxel dose was reduced to 30 mg/m^2 in the next cycle.

It was intended that all patients would receive at least three cycles unless their disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician decided to discontinue the treatment. Second-line chemotherapy or other treatments after this study were not restricted by the protocol.

Treatment Assessment

Baseline assessment included a physical examination, complete blood cell counts, hepatic and renal function tests, urinalysis, 12-lead electrocardiograph, and chest x-ray. Measurements of visible and palpable tumors were performed at baseline by chest x-ray, computed tomography scans, or magnetic resonance imaging scans. During the study, the medical history and results of physical examination, weight, vital signs, Eastern Cooperative Oncology Group PS, complete blood cell counts, and blood chemistry were monitored weekly, and urinalysis was performed every 3 weeks. Radiographic evaluation by computed tomography was performed to assess each patient's response to the treatment. Unidirectional measurements were undertaken using the new World Health Organization criteria (RECIST criteria).[14] Complete response (CR) was defined as the disappearance of all lesions, partial response (PR) was defined as a decrease of at least 30% in the sum of the longest diameter of the tumor, progressive disease (PD) was defined as an increase of at least 20% of the longest diameter of the tumor or the appearance of any new lesions, and stable disease was defined as any response other than CR, PR, or PD. Tumor response assessment was performed after every chemotherapy cycle.

Study Design and Statistical Analysis of the Phase II Trial

The primary objective of the trial was to determine response rate, defined as the proportion of the patients who attained CR or PR. Simon's two-stage optimal design[15] was used to determine the sample size and interim decision criteria. Assuming that a response rate of 40% in eligible patients would indicate potential usefulness, whereas a rate of 20% would be the lower limit of interest, with alpha = 0.05

TABLE 1. Patient Characteristics

	No. of Patients
Enrolled patients	50
Sex (male/female)	42/8
Median age (yr)	65
Age range (yr)	34–79
Performance status* (0/1/2)	21/28/1**
Histology	
Adenocarcinoma	30
Squamous cell carcinoma	11
Large cell carcinoma	9
Stage	
IIIB	8
IV	36
Postoperative recurrence	6

*Eastern Cooperative Oncology Group performance status; **ineligible case.

TABLE 2. Response Rate

Response	No. of Patients (%)
Complete response	0 (0)
Partial response	15 (30)
Stable disease	20 (40)
Progressive disease	15 (30)
Not evaluable	0 (0)
Overall response	15 (30)
95% confidence interval (%)	17.3–42.7

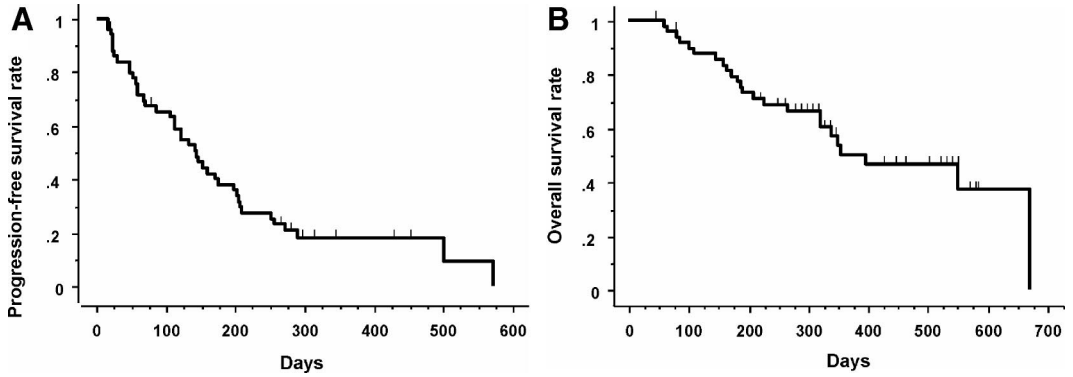

FIGURE 1. Progression-free survival (*A*) and overall survival (*B*) by the Kaplan–Meier method.

and beta = 0.10, 45 patients would be required. This regimen would be rejected when only 5 of the first 24 patients had an objective response at the interim analysis or when 13 of 45 patients had an objective response at final analysis. The secondary endpoint was toxicity and overall survival. Overall survival was defined as the interval between the start of treatment and the date of death or the last follow-up visit. Survival distribution was estimated by the Kaplan–Meier method.

RESULTS

Patient Characteristics

From October 2003 to February 2005, 50 NSCLC patients were enrolled from seven participating institutions. Patient characteristics are summarized in Table 1. More than half of enrolled patients had PS 1 (there was one case with PS 2), and 13 patients (26%) were elderly (≥70 years old). The predominant histology was adenocarcinoma (60%). Eight patients (16%) were stage IIIB, and six (12%) had postoperative recurrence with distant metastasis.

Tumor Response and Survival

Fifty patients received a total of 132 cycles of the protocol treatment; the median number of cycles was three (range, 1–6). All patients could be evaluated for response (Table 2). The overall response rate was 30% (95% confidence interval [CI] 17.3–42.7%). Stable disease was observed in 20 patients (40%), and PD was observed in 15 patients (30%). Among the 13 elderly patients, 7 (54%; 95% CI, 26.7–81.0%) experienced PR, whereas PR observed in younger patients was 8 (22%; 95% CI, 8.4–34.9%).

Survival analysis was performed in September 2005. The median follow-up for the living patients was 10.9 months

TABLE 3. Toxicities

Grade	0 No.	1 No.	2 No.	3 No.	4 No.	Grade 3/4 No. (%)
Hematologic						
Neutropenia	15	5	11	11	8	19 (38)
Febrile neutropenia	50	0	0	0	0	0 (0)
Anemia	5	19	16	9	1	10 (20)
Thrombocytopenia	21	16	8	4	1	5 (10)
Nonhematologic						
Anorexia	13	23	12	1	1	2 (4)
Nausea/vomiting	27	13	10	0	0	0 (0)
Fatigue	42	5	3	0	0	0 (0)
Diarrhea	46	4	0	0	0	0 (0)
Infection	48	0	2	0	0	0 (0)
Hiccoughs	45	5	0	0	0	0 (0)
Fever	36	9	5	0	0	0 (0)
Injection-site reaction	47	1	2	0	0	0 (0)
Alopecia	26	18	6	0	0	0 (0)
Edema	46	4	0	0	0	0 (0)
Neuropathy: sensory	43	7	0	0	0	0 (0)
Nail changes	47	1	1	1	0	1 (2)
ALT/AST	33	14	1	2	0	2 (4)
Sodium/potassium	37	10	0	2	1	3 (6)

(range, 1.4–19.1 months). The median progression-free survival time was 4.8 months (95% CI, 4.0–5.3) (Figure 1A). The median survival time (MST) of all patients was 11.8 months (95% CI, 11.3–18.4), and the 1-year survival rate was 50% (Figure 1B).

Toxicity

All patients were assessed for toxicity (Table 3). Of the 24 patients who received only one or two cycles, 15 terminated treatment because of their disease progression, and three patients discontinued chemotherapy because of toxicity. The most common hematological grade 3 or 4 adverse event was neutropenia (38%). Febrile neutropenia was not observed. Nonhematological toxicities were generally moderate. Anorexia of at least grade 3 was observed in only two patients (4%). One patient (2%) complained of grade 3 nail changes. Grade 3 elevation of transaminase occurred in two patients (4%). One patient developed grade 4 hyponatremia attributable to ADH secretion abnormality, although it is uncertain whether this had been caused by an adverse effect of treatment or paraneoplastic syndrome. No excessive lacrimation was observed.

DISCUSSION

Chemotherapy with a platinum-based regimen such as cisplatin is currently the standard regimen for advanced NSCLC. Cisplatin, however, is toxic for many patients, who therefore discontinue chemotherapy. The use of carboplatin instead of cisplatin has led to improvements in toxicity, with comparable efficacy. In advanced NSCLC, the aim of treatment is not only prolongation of survival but also maintenance of quality of life. Hence, it is important to develop effective regimens with low toxicity profiles. These regimens should also be suitable for outpatient-based chemotherapy.

In this study, we performed a phase II trial of biweekly docetaxel combined with carboplatin for patients with advanced NSCLC. We observed an overall response rate of 30%, a 1-year survival rate of 50%, and an MST of 11.8 months. In previous phase II studies using triweekly docetaxel plus carboplatin, the overall response rates were 42 to 44%, the 1-year survival rates were 53 to 53%, and the MSTs were 12.0 to 13.9 months.[8,9,16] Moreover, a recent randomized phase III study of docetaxel plus carboplatin showed an overall response rate of 24%, a 1-year survival rate of 38%, and an MST of 9.4 months.[7] Thus, the efficacy and the survival results of our biweekly regimen were comparable with those used in earlier studies.

Interestingly, we observed a high response rate (54%) in our elderly population, although this was only a result of subset analysis with small sample size. Patient characteristics such as PS or stage between younger patients and elderly patients were not different. Monotherapy of docetaxel has been shown to be a good option for chemotherapy in elderly NSCLC patients, according to a recent phase III trial[17]; thus, a randomized phase III study comparing our combination regimen with docetaxel alone for the elderly patients is warranted.

Regarding hematological toxicity, our patients experienced mild adverse effects. Triweekly docetaxel plus carboplatin induced neutropenia in about 70% of patients and febrile neutropenia in 3 to 15%.[6–9] In contrast, we observed grade 3 or 4 neutropenia in 38% of patients and no incidents of febrile neutropenia, suggesting that our biweekly regimen has a safer toxicity profile.

Nonhematological toxicities were mostly mild to moderate and manageable. The incidence of grade 3 or 4 nonhematological toxic effects was rare in this study (4% anorexia, 2% nail changes, 4% liver dysfunction, and 6% hyponatremia/hypokalemia). In contrast to previous findings, we did not observe any incidents of severe diarrhea or pulmonary toxicity.[7,9,12]

In conclusion, biweekly docetaxel combined with carboplatin had good efficacy and safety profiles compared with the standard combination of triweekly docetaxel and carboplatin. Although its efficacy was not superior to that of the standard regimen, its convenience and safety may be more suitable for outpatients, including elderly patients or patients with poor PS. Further trials, especially for elderly patients, are warranted.

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